UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,093	09/29/1999	KAZUHIRO OHSUYE	001560-373	5533

21839 7590 06/25/2002

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/25/2002 18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,093	OHSUYE ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed April 10, 2002 canceling claim 24, amending claims 1, 4 and 23 and adding claim 28 has been entered.

The Sequence Listing and the computer readable form thereof filed June 7, 2002 have been entered.

Claims 1-23 and 25-28 are pending.

Rejections and/or objections not reiterated from previous Office action are hereby withdrawn.

Drawings

The formal drawings filed on July 26, 2001 have been approved by Draftsman.

Specification

The instant disclosure contains sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. 37 CFR 1.821(d) requires the use of assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences. For example, on pages 8, 23, 24, 31, 33 and 34 sequences such as

RHHGP (if they are sequences and not abbreviations) are recited without sequence identifiers.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making GLP-1 and derivatives thereof, does not reasonably provide enablement for a process of making of any peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection was explained in the Office action mailed October 10, 2001. Following is a slightly reworded version thereof.

Claims 1-23 and 25-28 are directed to a method for producing a highly purified peptide. Therefore, they are drawn to a method of making of a genus of a polypeptide of an unknown function and having any characteristics. While the specification teaches a method of making of highly purified GLP-1 (7-37) and GLP-1(7-36) NH_2, it does not

provide any guidance as to a process for producing a highly purified peptide of any function and characteristics. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve experimentation to find the peptide that being attached to the peptide of interest would change characteristics of the latter, so that it would become possible to use this characteristics in various purification techniques.

The state of the art is such that it is unpredictable which helper should be used for each peptide of interest, to enable the claimed method for any peptide of interest, and the specification provides no guidance on the matter.

It is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. Consequently, excessive trial and error experimentation would be required to identify the necessary helper sequence that would impart the properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted *a priori*. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest. Furthermore, the development of an

appropriate purification scheme for a peptide with known characteristics requires additional trial and error experimentation.

Therefore, one skilled in the art would require guidance as to how to make a highly purified peptide of any function and structure by a claimed process. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 and 25-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing because it appears to be directed to two distinct processes of making two distinct products: 1) a peptide of interest that has a helper peptide added thereto, or 2) a fusion protein that has a protective peptide further added to the peptide of interest that has a helper peptide added thereto. Claims 2-23 and 25-28 are rejected as dependent from claim 1.

Claim 23 is unclear because claim 1 refers to the purification of "the peptide of interest" not to "the final purified product" comprising endotoxin.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13, 18-23 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Tarnowski et al.

Tarnowski et al. (US Patent 5,202,239, form PTO-1449) teach a method for producing a peptide by expressing a peptide as fusion protein having a high pI, separating the fusion proteins from all other host cell proteins, and separation of the carrier from the peptide after cleavage (abstract, column 1, lines 40-58, claims 1-8).

Claims 1-13, 18-23 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Yabuta et al.

Yabuta et al. (US Patent 5,670,340, form PTO-1449) teach a method for producing peptides by expressing peptides as fusion proteins comprising a protective peptide, a fragment of *E. coli* β-galactosidase, a linker and a peptide of interest wherein the protective peptide and a linker are selected so that pI of the fusion protein is between 4.9 and 6.9 (abstract, claims 1-5).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarnowski et al. in view of Bell et al.

The teachings of Tarnowski et al. are outlined above.

Bell et al. teach GLP-1 and its physiological importance.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Tarnowski et al. to the expression of GLP-1.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuta et al. in view of Bell et al.

The teachings of Yabuta et al. are outlined above.

Bell et al. teach GLP-1 and its physiological importance.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Yabuta et al. to the expression of GLP-1.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tarnowski et al. in view of Mojsov et al.

The teachings of Tarnowski et al. are outlined above.

Mojsov et al. teach a natural derivative of GLP-1(7-37), GLP-1 (7-36)NH_2, and its physiological importance.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Tarnowski et al. to the production of a highly purified GLP-1 and than to make an amidated form thereof, physiological importance of which is taught by Mojsov et al.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuta et al. in view of Mojsov et al.

The teachings of Yabuta et al. are outlined above.

Mojsov et al. teach a natural derivative of GLP-1(7-37), GLP-1 (7-36)NH_2, and its physiological importance.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Yabuta et al. to the production of a highly purified GLP-1 and than to make an amidated form thereof, physiological importance of which is taught by Mojsov et al.

Response to Arguments

Applicant's arguments filed April 10, 2002 have been fully considered but they are not persuasive.

With regard to the specification Applicants provided the Sequence listing comprising sequence RHHGP as SEQ ID NO: 25. However, the specification recites "a fusion protein ... referred to hereinafter as RHHGP[G]" (e.g., page 21, lines 5-13). Therefore, it is unclear whether "RHHGP" is a sequence or an abbreviation. In the former case the specification must be amended to insert the reference to the sequence identifier, *supra*.

With regard to the 112, 1st paragraph, enablement rejection Applicants argue that "the claimed method is used to overcome general problems in the art, not problems related to specific peptides of interest. ... the specification in fact identifies many peptides which can be used as the peptide of interest for the present invention, for example, on page 10, line 34-page 11, lines 1 to 27" (Remarks, page 7, last paragraph). This is not persuasive because there are many "general problems in the art" and they require different solutions. The invention is aimed at overcoming "the problems possessed by the protein of interest, such as insolubility of the peptide, gel-formation, etc., during purification and other downstream processing" (page 10, 2nd paragraph). However, different problem may or may not have different solution. The specification suggests that "general problems" which are different for different peptides

can be overcome by producing a fusion of a peptide of interest with another peptide, so that "the problems possessed by the protein of interest" would be overcome. However, the specification provides no guidance as to what peptide should be linked to a peptide of interest, so that a highly pure peptide of interest could be obtained. Applicants argue that "the peptide of interest for the present invention, [is identified] for example, on page 10, line 34-page 11, lines 1 to 27". This is not persuasive because the limiting point of the claimed invention is not a peptide of interest per se but a helper peptide that would impart the requisite properties to the fusion peptide in a given case. No other helper peptide and fusion protein with another peptide of interest but GLP-1 is disclosed. It is unclear, whether applicants imply that peptides recited on the above pages can substitute for GLP-1 in the disclosed invention. Applicants further argue that "the specification describes the physico-chemical properties to be considered to select combinations of peptides of interest and helper peptides. *See*, page 5, lines 6-15" (page 8, 2nd paragraph). This is not agreed with because the specification on page 5, lines 6-15, does not go beyond merely stating that "it is an object of the present invention to provide a process for producing a peptide of interest in an efficient manner by relieving the problems derived from the physicochemical properties of the peptide of interest itself ..." (emphasis added). The specification provides no common solution for every general problem of every peptide and there is none. Each peptide requires an individual approach to develop an appropriate fusion protein and purification scheme.

With regard to the 102 rejection applicants argue that "by contrast with Tarnowski et al and Yabuta et al, according to the present invention, a fusion protein comprising (1) a peptide of interest, (2) a helper peptide and (3) a carrier protein is expresed. Next, the fusion protein is cleaved to liberate an intermediate(precursor) peptide comprising (1) a peptide of interest and (2) a helper peptide, and the liberated intermediate peptide is purified. After that, the intermediate peptide is cleaved so as to liberate (1) a peptide of interest" (paragraph bridging pages 9 and 10). This is not persuasive because it appears that applicant's invention is the finding that the addition of an extra peptide to the fusion protein renders the easy and efficient purification of a peptide of interest. That is not the case. Further, the instant claims does not require the fusion protein to comprise three peptides but only two, see claim 1. Furthermore, the linker in the Yabuta et al. patent can be considered as an additional peptide. Applicants continue to argue that "by failing to describe or even suggest the use of a helper and a carrier protein, as well as a process wherein an intermediate peptide comprising the peptide of interest and a helper peptide are purified and then cleaved to liberate the peptide of interest, Tarnowski et al. and Yabuta et al. fail to anticipate the claimed invention" (page 10, 3rd paragraph). This is not agreed with because while not using the terms helper and carrier as they are applied in the instant invention, they teach the main aspect of the invention, changing the properties of a peptide of interest by adding another peptide thereto, so that the fusion has the requisite properties. They further

teach separation (purification) of said fusion followed by a cleavage and purification of a peptide of interest.

With regard to the 103 rejection applicants argue that" the teachings of Bell of GLP-1 together with the teachings of Tarnowski et al. and Yabuta et al. thus fail to teach or even suggest the instantly claimed methods wherein GLP-1 is the peptide of interest" (page 11, 2nd paragraph). This is not persuasive because as a secondary reference in a 103 rejection, the Bell et al. reference does not have to disclose the same invention but only to make it obvious. In their Remarks, Applicants argue that their methods are applicable to any known peptide. The methods as claimed are not found to be novel for the reasons discussed above. Therefore, to apply a known method to a known peptide is obvious.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

a shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

June 20, 2002